A Review of the United Kingdom Prospective Diabetes Study (UKPDS) and a Discussion of the Implications for Patient Care

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Introduction

Diabetes Mellitus is a chronic illness that increases the risk of microvascular complication and results in blindness, kidney failure, and lower extremity amputations, and macrovascular complication of coronary artery disease and stroke. In the State of Hawaii, an estimated eight to ten percent of the population have diabetes mellitus, i.e. about 80,000 to 100,000 individuals, primarily adults with type 2 diabetes. Alarmingly, native Hawaiian adults over 30 years of age have been identified with a diabetes prevalence rate of 20%. Several studies clearly document the increasing rate of diabetes among native Hawaiians over the past 30 years. Based on recent data, it is estimated that about 20,000 adult native Hawaiians (18-20% prevalence rate) have diabetes mellitus.[1] It would appear that interventions to prevent diabetes and diabetic complications receive the highest priority in the effort to improve the health status of the people of Hawaii, especially native Hawaiians.

Two major intervention trials have clearly demonstrated that intensive glycemic control prevents and delays the development of microvascular complication in patients with type 1 diabetes: the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study (SDIS).[2,3] Results from a randomized prospective 6-year study in Japan show that intensive insulin treatment of type 2 diabetic patients reduces microvascular complication.[4] Many studies have demonstrated the association of hyperglycemia with macrovascular complications of ischemic heart disease and stroke and increased cardiovascular disease risk factors, e.g., dyslipidemia, hypertension, and obesity. The 12-year cardiovascular mortality of men screened in the Multiple Risk Factor Intervention Trial (MRFIT) showed that diabetic patients consistently had higher cardiovascular mortality than non-diabetic men matched for one or more of the major risk factors for CVD.[5] The data from the MRFIT study suggests that glycemic control in type 2 diabetes is an important and independent risk factor for CVD. Still, results of randomized controlled clinical trials that examines the effect of normalized blood glucose levels in type 2 diabetic patients on macrovascular endpoints have been inconclusive and somewhat controversial.[6,7]

The United Kingdom Prospective Diabetes Study (UKPDS) is the longest and largest prospective clinical study of type 2 diabetics. Started in 1977, newly diagnosed type 2 diabetic patients were recruited. The aim was to determine whether an "active" pharmacological program (intensive) of hyperglycemic management results in a better long-term outcome than a diet and exercise program (conventional).

The UKPDS was designed to answer the following questions:

1) If high blood glucose levels are more intensively treated in people with type 2 diabetes, could serious complications of diabetes be prevented or delayed, and are there any advantages or disadvantages of the various pharmacological interventions that lower blood glucose levels?
2) Would intensive treatment of high blood pressure in type 2 diabetic patients reduce the risk of diabetes complications, and are there any advantages or disadvantages of the various pharmacological interventions that lower blood pressure?

UKPDS Study Design and Results

Between 1977 and 1991, 7616 patients with newly diagnosed type 2 diabetes, ages 25-65 were referred by general practitioners to the 23 participating UKPDS hospitals, and 5102 patients were recruited into the study. After a 3-month diet program, 4209 patients were enrolled into the study of which 3867 patients who had a mean fasting plasma glucose concentrations of 6.1-15 mmol/L (110–270 mg/dl) were randomly assigned to sulfonylurea (chlorpropamide, glibenclamide, glipizide), insulin, and conventional treatment groups (baseline characteristics are presented in Table 1). Patients in the conventional treatment group attended clinic every 3 months and received dietary counseling with the aim of maintaining near-normal body weight and maintain FPG levels below 15 mmol/L (270 mg/dl) without symptoms of hyperglycemia. If marked hyperglycemia or symptoms occurred, patients were secondarily randomized to sulfonylurea, insulin or metformin treatment. There were three measures of outcomes for comparison between conventional and intensive treatment; 1) any diabetes-related endpoint (sudden

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death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction), 2) diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death), and 3) all-cause mortality.

Table 1. Baseline characteristics of patients in conventional and intensive-treatment groups

Character	Conventional (n=1138)	Intensive (n=2729)
Age	53.4	53.2
Sex		
Male/Female	705/433	649/444
Ethnicity		
(%Caucasian)	81	81
Weight (kg)	78.1	77.3
Body mass index (kg/m2)	27.8	27.5
Blood Pressure	135/82	135/83
Fasting plasma glucose(mmol/L) (mg/dl)	8.0 (7.1-9.6)	8.1 (7.1-9.8)
HbA1C	7.05	7.09
LDL cholesterol (mmol/L)	3.5	3.5
Serrogate clinical endpoints		
Retinopathy (%)	36	36
Proteinuria (%)	2.1	1.7
Plasma Creatinine (mmol/L) (mg/dL)	81 (66-99) 0.92	82 (67-100) 0.93

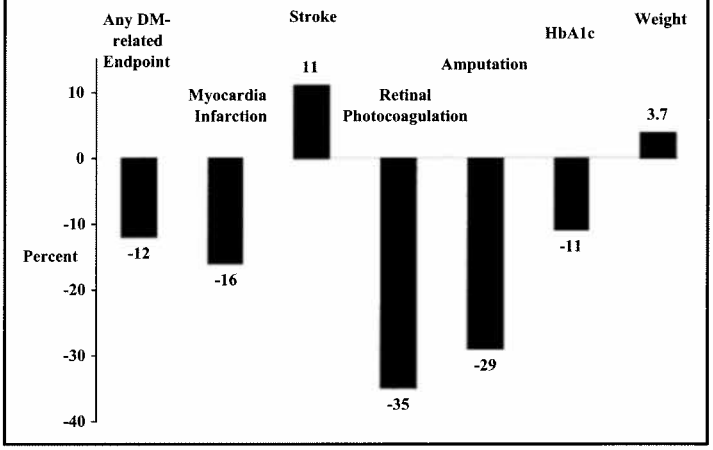
Intensive treatment with sulfonylureas and insulin[8]

The FPG and HbA1c levels in the conventional group increased steadily from the beginning of the study compared to the intensive group which had an initial decline in FPG and HbA1c levels within the first year, but subsequently increased with time similar to that seen in the conventional group. Median HbA1c for each 5-year period of follow-up in the intensive and conventional groups were 6.6% and 7.4% respectively for the first period, 7.5% and 8.4% for the second, and 8.1% and 8.7% for the third period. The median 10-year HbA1c values with chlorpropamide (6.7%), glibenclamide (7.2%), or insulin (7.1%) treatments were each significantly lower than with conventional treatment (7.9%).

The data from 2729 patients intensively treated with sulfonylureas and/or insulin achieved an average HbA1c level of 7% (6.2-8.2) over 10 years and showed a 12% lower rate of diabetes-related endpoints than 1138 patients treated with conventional diet and exercise program with an average HbA1c level of 7.9% (6.9-8.8). Most of the risk reduction was attributed to the 25% lower rate of microvascular endpoints; retinopathy (requiring photocoagulation) and albuminuria (Figure 1). There was a 16% reduction in myocardial infarction rate in the intensive treatment group as compared to the conventional group, but this difference was not statistically significant (p=0.06). Differences in any microvascular or macrovascular endpoint were not observed between the three agents used in the intensive treatment group with the exception of the chlorpropamide treatment group which failed to show reduced rate of retinopathy requiring photocoagulation.

As expected, patients in the intensive treatment group had significantly more hypoglycemic episodes than patients in the conventional group. The rates of major hypoglycemic episodes (reactions requiring assistance from others for recovery) per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin. Additionally, there was significant weight gain in the intensive group (mean 2.9 kg) than in the conventional group (p<0.001), and patients assigned to insulin therapy had greater gain (4.0 kg) than those assigned chlorpropamide (2.6kg) or glibenclamide (1.7kg).

Figure 1. Relative Risk Reduction of the Aggregate and Single Endpoints of Intensive versus Conventional Treatment



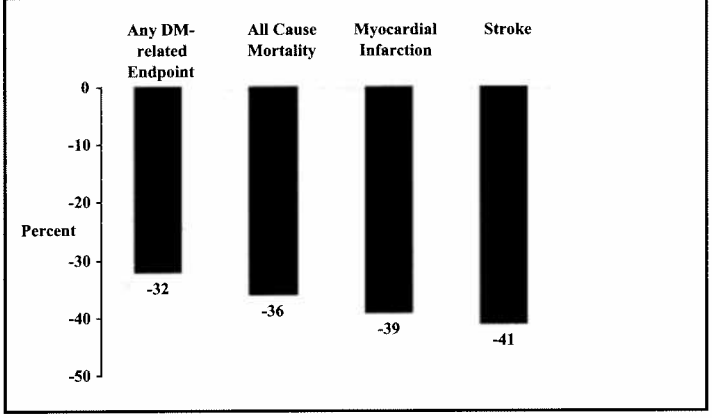
Metformin treatment in overweight patients[9]

Insulin resistance is a key feature of type 2 diabetes, especially when obesity is present. Metformin is a biguanide that decreases blood glucose concentration by mechanisms different from those of sulfonylurea or insulin yet poorly understood. Treatment with metformin results in suppression of endogenous hepatic glucose production and enhanced glucose uptake by muscle [10]. In the UKPDS, 1704 newly diagnosed, overweight (> 120% ideal body weight) type 2 diabetic patients were randomized to receive either conventional treatment, primarily diet control (n=411), or treatment with metformin (n=342), chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). Treatment in the metformin group was started with one 850 mg tablet per day, then twice a day and then 1700 mg in the morning and 850 mg with the evening meal. In the metformin group, there was a decrease in FPG and HbA1c levels in the first year, with a subsequent gradual rise in both variables. The median HbA1c level during the 10 years of follow-up was 7.4% in the metformin group and 8.0% in the conventional group. The metformin group showed significant 32% lower risk of any diabetes-related endpoint, including a 36% reduction in diabetes-related death and all-cause mortality as compared to the conventional group. Furthermore, a significant lower risk of myocardial infarction (39%) and macrovascular diseases (30%) in the metformin group (myocardial infarction, sudden death, angina, stroke, and peripheral disease) was observed (Figure 2). Similar macrovascular complication risk reduction was seen in the metformin group as compared to the sulfonylurea or insulin

groups. The rate of major hypoglycemic episodes was lower than patients taking sulfonylureas (1.2% in chlorpropamide group, 1.0% in glibenclamide group, 2.0% in insulin group and 0.6% in metformin group). There was no significant change in body weight between metformin group and conventional group.

Additional 1234 patients, both non-overweight and overweight, who were initially started on sulfonylurea therapy, were randomly assigned to early addition of metformin or continued sulfonylurea treatment if blood glucose profiles deteriorated. The comparison of the combination treatment arms with and without the addition of metformin to sulfonylurea-treated patients produced some unexpected findings. The addition of metformin to sulfonylurea was associated with a 96% increased risk of diabetes-related death and 60% all-cause deaths as compared to the sulfonylurea only group. The investigators completed a meta-analysis and an epidemiological analysis of these results and could not substantiate the finding. Still, the data demonstrated a nearly two fold increase in mortality with combination metformin-sulfonylurea therapy irrespective of glycemic control.

Figure 2. Relative Risk Reduction in the Incidence of Clinical Endpoints of Metformin versus Conventional Treatment



Blood pressure control and diabetic complication1[11,12]

The UKPDS also compared macrovascular and microvascular complications with blood pressure control in a subgroup of 1,148 hypertensive type 2 diabetic patients. 758 patients were allocated to a "tight" control group aimed to keep blood pressure < 150/85 mm Hg, and 390 patients to a "less tight" control group targeting blood pressure < 180/105 mm Hg. Captopril, an Angiotensin Converting Enzyme (ACE) inhibitor or atenolol, a selective β-adrenergic blocking agent was the anti-hypertensive medications used in this study. 400 patients were given 50 mg twice daily of captopril with a starting dose of 25 mg twice daily, and 358 patients were treated with a daily dose of 50 mg atenolol, which was increased to 100 mg as necessary. If blood pressure goals were not met in either medication group, the other agent was added to the regimen.

During the median follow-up period of 8.4 years, mean blood pressure in the "tight" blood pressure group was 144/82 mm Hg compared with 154/87 mm Hg in the "less tight" control group. The "tight" control group had a 24% reduction in diabetes-related endpoints; 32% reduction in deaths due to diabetes, 44% fewer strokes, and 37% fewer microvascular endpoints, primarily the number of retinal photocoagulation and the development of diabetic maculopathy, which is the main cause of visual impairment in type 2 diabetes. This finding from the UKPDS is the first known report in type 2 diabetes which demonstrate that interventions offering "tight" blood pressure control reduces the risk of diabetic complications.

The results of blood pressure treatment with captopril or atenolol failed to show specific advantages or disadvantages in preventing the complications of type 2 diabetes. There was a 37% progression rate for retinopathy in each group compared to a rate of 51% in the "less tight" control group, and differences were not observed between the captopril and atenolol groups for deterioration of visual acuity. The progression rate of albuminuria and proteinuria and the occurrence of two-fold increase in plasma creatinine concentration and end stage renal disease were similar between these two medication groups. After the first four years of treatment, more patients in the atenolol group discontinued medication, because of impaired peripheral circulation or bronchospasm. Four percent of patients in the captopril group discontinued treatment because of side effects with coughing, and the ACE inhibitor were withdrawn in five patients due to increasing creatinine levels. There was no differences found in the incidence of myocardial infarction, strokes, heart failure, or angina between the two medication groups.

Implications for Patient Care

The UKPDS is a landmark study of type 2 diabetic patients producing very useful data that is translatable to clinical practice. This study has shown that "tight control" of blood glucose levels in type 2 diabetic patients will dramatically reduce the incidence of microvascular complications. Many prospective studies have suggested that hyperinsulinemia is a risk factor for cardiovascular disease in people without diabetes, although these studies do not distinguish between insulin and insulin resistance as the factor associated with increased cardiovascular risk. The University Group Diabetes Program (UGDP), a similarly large prospective study (1,027 patients enrolled) was conducted during a period between 1960- 1966 to evaluate the efficacy of glycemic control in type 2 diabetes in the prevention of cardiovascular complication.[13] The result of the UGDP study was highly controversial because it failed to demonstrate any benefit from oral hypoglycemic agent and insulin therapies. Moreover, the data from UGDP study showed a significantly higher cardiovascular mortality rate in the tolbutamide-treated group than in the placebo-treated group. Over the years, this unexpected finding has elicited many hypotheses that could explain the tolbutamide effect. The mechanism of sulfonylurea toxicity includes myocardial damage from inhibition of ATP-K+ channel opening in the presence of myocardial ischemia due to sulfonylurea binding to the cardiovascular SUR2 receptor, an event that could also increase the likelihood of ventricular arrhythmia.[14] The UKPDS did not demonstrate specific adverse cardiovascular effects with chlorpropamide, glibenclamide, or insulin treatment. Thus, the UKPDS appears to clearly dispel the notion of cardiovascular disease toxicity with sulfonylurea or insulin therapy.

The most striking and unexpected finding from the UKPDS is the results from obese type 2 diabetic patients. Metformin treatment

reduced diabetes-related endpoints, diabetes-related death, and all-cause mortality when compared with conventional treatment. Given the same HbA1C levels obtained the effect of metformin in reducing the risk for diabetes-related complication and all-cause mortality is difficult to explain on the basis of glycemic control. The improvements in cardiovascular disease outcomes might be due to anti-atherogenic effects with metformin, which includes improved fibrinolysis, decreased platelet aggregation, increased erythrocyte deformability, and decreased lipid incorporation into vessel walls which might explain the decreased arterial wall smooth muscle cell growth, and restoration of arterial vasodilatation. The investigators of the UKPDS "boldly" concluded that metformin might be considered first-line treatment in overweight type 2 diabetic patient. The results of metformin treatment suggest that thiazolidinediones (a new class of anti-hyperglycemic agents), which also enhances insulin sensitivity, could produce similar results.[15] The use of metformin in combination with a sulfonylurea has shown an increase in risk of diabetes-related and all-cause mortality. This contradictory and controversial finding may be a consequence of the analytical strategy and have raised new questions for the next generation of clinical trials.[16] The contradiction in the results is the finding of increased mortality with combined used despite clearly reduced morbidity and mortality when used separately. The controversial consideration is the fact that many physicians are now using this combination for patients with diabetes who failed to reach targeted goals with one agent. American Diabetes Association believes this analytical approach does not resolve the discrepancy in the results with metformin, that is, it does not provide assurance that the combination is safe or prove that it is unsafe. If there is some specific mechanism of adverse interaction between metformin and sulfonylurea drugs, this can only be definitely determined in a new, appropriately designed, randomized, placebo-controlled trial. Until such a trial is concluded, American Diabetes Association does not recommend any change in the current guidelines for the use of metformin as monotherapy or in combination with sulfonylurea drugs.[17]

In addition to adequate control of blood glucose levels, aggressive control of blood pressure has shown positive effect in all diabetes-related complications. Hypertension is one of the risk factors for cardiovascular and renal disease and commonly associated with type 2 diabetes. At the age of 45 years, approximately 40% of patients with type 2 diabetes are hypertensive and this proportion rises to an estimated 60% prevalence by age 75 years. The negative inotropic effect of atenolol might have been expected to increase the incidence of heart failure, but the protection against heart failure was the same for atenolol as for captopril. The similar effect of captopril and atenolol on clinical endpoints suggests either that both β-adrenergic blockers and ACE inhibitor have specific beneficial effects or that the decrease in blood pressure is the important factor and not the type of treatment. These results are interesting given the current debate over benefit from ACE inhibitor treatment for preventing the progression of diabetic nephropathy. The suggestion that ACE inhibitors have a specific renal protective effect in the treatment of type 2 diabetes is not supported in this study. These results clearly demonstrate the renal protective effect of reducing blood pressure, which decrease capillary perfusion, transcapillary leakage of albumin, and decrease damage to glomeruli. This study shows that atenolol and captopril are equally effective and safe in lowering blood pressure and reducing the risk of complications in type 2 diabetic patients. In the UKPDS, lipid levels were not included in the data analysis and may prove to be a contributing factor to some of the results presented.

In summary, how do we translate the UKPDS results? The American Diabetes Association believes that the evidence confirms what many investigators have suspected all along that people with type 2 diabetes and their health care teams should strive diligently to lower blood glucose levels as close to normal as possible. Thus, intensive therapy of type 2 diabetes with sulfonylureas and insulin is beneficial despite the associated weight gain, and not a detriment to reducing cardiovascular outcomes. The UKPDS data supports the use of metformin as a starting agent in overweight patients as monotherapy and perhaps could be extended to other insulin sensitizers, the thiazolidinedione.

The importance of controlling cardiovascular disease risk factors in diabetic patients cannot be over emphasized, especially blood pressure control as reported in the UKPDS. Still, the finding of equal efficacy between captopril and atenolol does not fully support the abandonment of ACE inhibitors for cheaper, generic β-adrenergic blockers in treating hypertension among diabetics. Along with the potential renal protective effect of ACE inhibitors, these agents minimally affect plasma lipid levels, enhances myocardial contractility in CHF that is commonly seen in diabetes, and does not induce bronchospasm. American Diabetes Association concluded that both drugs used to reduce hypertension are equally effective and safe, and either can be used with great benefit to treat uncomplicated hypertension in patients with type 2 diabetes. Both conventionally and intensively treated patients in the blood glucose study equally benefited from blood pressure lowering. Likewise, the tightly and less tightly controlled blood pressure study patients had equal benefit from blood glucose lowering. Thus, both hyperglycemia and hypertension should be vigorously treated when they occur together with an expectation that reductions in microvascular and cardiovascular outcomes will be additive [17]. Lastly, other cardiovascular disease risk factor analysis (e.g. dyslipidemia, cigarette smoking, nutrition and exercise modification) should also be emphasized since the clinical management of type 2 diabetes requires a multimodal and comprehensive approach.

What is clear from the UKPDS is that hyperglycemia treatment impacts microvascular and macrovascular outcomes in patients with diabetes, even with less than a one percent reduction in HbA1c levels. The UKPDS findings more clearly demonstrate the importance of addressing the other CVD risk factors in type 2 diabetes mellitus to reduce secondary complications. The results from the UKPDS define the management of type 2 diabetes mellitus as a complex disorder, engaging the physician to examine more of the patient than hyperglycemia.

References

1. Beddow R, Arakaki R. Non-Insulin Dependent Diabetes Mellitus: an Epidemic Among Hawaiians. *Hawaii Med J* 1997;56:14,16-17.
2. DCCT Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial. *N Engl J Med* 1993;329:978-86.
3. Reichard P, Nilsson BY, Rosenqvist U. The effect of long term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304-309.

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4. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabet Res Clin Pract* 1995;28:103-17.
5. Stamler, J, Vaccaro, O, Neaton, JD, et al. For the Multiple Risk Factor Intervention Trial Research Group: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-444.
6. Klein, R, Klein, BEK, Moss, SE, et al. Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. *Arch Intern Med* 1994;154:2169-2178.
7. Abraira, C, Colwell, JA, Nuttall, FQ, et al. And the VA CSDM Group. Veterans affair cooperative study on glycemic control and complications in type 2 diabetes (VA CSDM). Results of the feasibility trial. *Diabetes Care* 1995;18:1113-1123.
8. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
9. UKPDS Group. Effect of intensive blood-glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
10. Henry RR. Type 2 diabetes care: the role of insulin-sensitizing agents and practical implications for cardiovascular disease prevention. *Am J Med* 1998 Jul 6;105(1A):20S-26S.
11. UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 1998;317:703-713.
12. UKPDS Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). *BMJ* 1998;317:713-20.
13. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult onset diabetes. *Diabetes* 1970;19(suppl2):747-830.
14. Scheen AJ, Lefebvre PJ. Oral antidiabetic agents. A guide to selection. *Drugs* 1998 Feb; 55(2):225-36.
15. Bloomgarden ZT. International Diabetes Federation meeting, 1997. Issues in the treatment of type 2 diabetes; sulfonylureas, metformin, and troglitazone. *Diabetes Care* 1998 Jun;21(6):1024-6.
16. Nathan DM. Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study (comment). *Lancet* 1998;352:832-33.
17. American Diabetes Association: clinical practice recommendations 1999. *Diabetes care* 1999; 22 Suppl 1:S1-114.

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